Office Action Summary	Application No.	Applicant(s)	
	10/562,746	HUMPRHEYS ET AL.	
	Examiner	Art Unit	
	CHUN DAHLE	1644	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 November 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) *4-7,10,11,18-25 and 28-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,8,9,12-17,26,27 and 37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *04/30/2008*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *20100308* .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election without traverse of Group I (drawn to an antibody Fab fragment) and species of SEQ ID NO:2, filed on July 16, 2009, is acknowledged.

With respect to the interchain cysteine position, applicant initially elected interchain cysteine at position 127 of the heavy chain (see Response To Restriction Requirement filed on July 16, 2009). During a telephone conversation with applicant's representative, Sandra Weiss on March 11, 2010, applicant indicated that she would like to elect interchain cysteine at position 233 of the heavy chain and that SEQ ID NO:1 would read on the interchain cysteine elected. As such, the species of the interchain cysteine under consideration would be at position 233 rather than 127. The Examiner thanks applicant for timely clarifying this issue.

Claims 1-37 are pending.

Claims 4-7, 10, 11, 18-25, and 28-36 have been withdrawn from further consideration, under 37 CFR 1.142(b), as being drawn to nonelected invention.

Claims 1-3, 8, 9, 12-17, 26, 27, and 37 are currently under consideration as they read on the elected invention of an antibody Fab fragment comprising a heavy chain constant region that terminates at inter chain cysteine of position 233 of the CH1 and wherein the heavy chain constant region comprises a sequence having at least 90% identity to SEQ ID NO:1 and a light chain constant region comprises a sequence having at least 90% identity to SEQ ID NO:2.

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 3 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 3 is indefinite in that they only describe the number of cysteine position without reciting the numbering system.

It is suggested that applicant amend the claim to recite the particular numbering system used (e.g. Kabat numbering system as disclosed on page 3 of the specification).

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 8, 9, and 37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

A) Claims 8 and 9 recites "wherein the heavy chain constant region comprises a sequence having at least 90% identity or similarity to the sequence of SEQ ID NO:1" and "wherein the light chain constant region comprises a sequence having at least 90% identity or similarity to the sequence o f SEQ ID NO:2", respectively.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The disclosure appears to show only Fab comprising heavy chain constant region of SEQ ID NO:1 and light chain constant region of SEQ ID NO:2 (e.g. see Example 1 on pages 18-19). The specification does not provide sufficient guidance or direction as to which amino acid residues in SEQ ID NOs 1 or 2 can be altered to maintain the functions of the claimed Fan antibody fragment. The instant claims encompass in their breadth *any* Fab fragment "wherein the heavy chain constant region comprises a sequence having at least 90% identity or similarity to the sequence of SEQ ID NO:1" and "wherein the light chain constant region comprises a sequence having at least 90% identity or similarity to the sequence o f SEQ ID NO:2".

It was well known in the art at the time of the invention that constant domain structure of an antibody would affect the antibody function. For example, Lazar et al. (WO 03/074679) teach that the determinants of antibody properties, such as stability, solubility and affinity for antigen, important to its functions are overlapping; thus engineering an antibody to be more soluble may cause a loss in affinity for its antigen (see entire document, particularly page 3). Further, Pritsch et al. (J. Clin. Invest. 1996 98;10:2235-2243) teach CH1 domain can affect antigen binding of an Fab fragment (e.g. see Discussion on pages 2240-2243). As such, without guidance as to which residues in SEQ ID NOs: 1 or 2 can be changed to maintain the same function of the claimed Fab fragment, one of skill in the art would not know how to make and/or use an Fab fragment comprising at least 90% identity or similarity to either SEQ ID NO:1 or SEQ ID NO:2 as claimed.

In the absence of sufficient guidance, or working examples, the effect of Fab comprising an heavy chain constant region and/or a light chain constant region comprising sequences of at least 90% identical and/or to SEQ ID NOs:1 and 2 on Fab function is unpredictable; thus the experimentation left to those skilled in the art, is unnecessarily, and improperly, extensive and undue.

B) Claim 37 is drawn to a pharmaceutical composition comprising an antibody Fab fragment without setting forth any antigen specificity.

It is noted that the recited "pharmaceutical composition" has the intended uses for prevention, diagnosis or treatment of diseases in human and animals. Thus, to enable such claims, the specification must teach how to use the composition without undue experimentation for prevention, diagnosis, and treatment of diseases in human and animals. However, the instant specification fails to teach how to use a "pharmaceutical composition" as claimed. The uses of monoclonal antibodies in a pharmaceutical composition are unpredictable as evidenced by following references:

For example, Vitetta et al. (Science 2006 313:308-309) teach that given the complex structure of antibodies, designing therapeutic antibodies can be unpredictable; in the case of anti-CD28 antibody, healthy humans injected with the anti-CD28 antibody suffered immediate and profound side effects (see pages 308-309).

Therefore, it is unpredictable whether an Fab fragment with any or all antigen specificity (e.g. anti-CD28 antibody) can be formulated into pharmaceutical composition for the intended uses for prevention, diagnosis or treatment of diseases in vivo.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Without sufficient guidance, it is unpredictable and would require undue experimentations for one of skill in the art to determine which monoclonal antibodies can be formulated into a pharmaceutical composition for the intended uses of prevention, diagnosis or treatment of diseases in human and animals since not all monoclonal antibodies can be used in vivo.

In view of the quantity of experimentation necessary, the limited working example, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

Deleting the word "pharmaceutical" would obviate this rejection.

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1-3, 8, 9, 12, 13 and 37 are rejected under 35 U.S.C. 102(b) as being anticipated by Carter et al. (WO 93/06217, reference on IDS).

Carter et al. teach Fab' fragments comprising CH1 and CL1 wherein the CH1 is terminated at hinge cysteine residue at the C-terminus and wherein the cysteine is the at the same position as disclosed by the instant specification based upon Kabat numbering (e.g. see pages 5-7 and pages 11-12 and 19). Cater et al. further teach that one or both said cysteines can be modified with chemical groups (e.g. see 16-17) and cytotoxins (e.g. see pages 27-28) that is considered as effector molecules. Furthermore, Carter et al. teach pharmaceutical composition comprising said Fab' fragments in well known carriers (e.g. see pages 27-28).

Given the well known conserved nature of antibody constant regions and the recited "90% identity or similarity" in claims 8 and 9, the prior art's Fab' comprising CH1 and CL1 would be considered to be inherently comprising the sequences that are "at least 95% identity or similarity to" the claimed SEQ ID NOs: 1 and 2.

Therefore, the reference teachings anticipate the claimed invention.

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1, 12-17, 26, and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carter et al. (WO 93/06217, reference on IDS) in view of Chapman et al. (Nature Biotechnology, 1999 17:780-783).

The teachings of Carter et al. have been discussed, supra. Carter et al. further teach that the Fab' fragments offer advantages of homogeneity and purity (e.g. see Abstract).

The reference teachings differ from the claimed invention by not describing one or more effector molecules attached to cysteines to the light chain constant region and the heavy chain constant region.

Chapman et al. teach that therapeutic antibody fragments including Fab's can be modified by conjugating PEG molecule to the specific sites at hinge cysteine residues (e.g. see page 780). Chapmen et al. teach that the hinge cysteine residues are particularly suitable for attaching PEG because they are well away form antigen-binding region; thus, modifications involving these cysteine residues would not affect the antigen binding of the Fab' fragments (e.g. see right column on page 780). Chapmen et al. further teach

modification with PEG can enhance the half-lives of the Fab' progressively as more PEG molecules attached (e.g. see Tables 2 and 3 on page 782).

It would thus be obvious to one of skill in the art at the time of the invention to combine the teachings of Carter et al. and Chapman et al. to produce Fab' that terminates at hinge cysteine and conjugate one or more PEG to the cysteine residues because the Fab' fragments offer advantages of homogeneity and purity and conjugating PEG to cysteine residues (e.g. hinge cysteine) can prolong serum half-lives of therapeutic antibody fragment. Given the teachings of Carter et al. regarding Fab' with cysteine at the C-terminus of the CH1 and the disclosure of Chapman et al. pertaining to Fab'/PEG conjugate at the hinge cysteine residues, a person of ordinary skill in the art would have been motivated to combine the teachings of the prior art to achieve the claimed product and that there would have been a reasonable expectation of success.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chun Dahle whose telephone number is 571-272-8142. The examiner can normally be reached on 8:30-5:00. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Ram Shukla can be reached 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Chun Dahle/
Examiner, Art Unit 1644